AMINOSYN-HF - isoleucine, leucine, lysine acetate, methionine, phenylalanine, threonine, tryptophan, valine, alanine, arginine, glycine, histidine, proline, serine and cysteine hydrochloride injection, solution
Hospira, Inc.

Flexible Plastic Container
Avoid exposure to light until use
Hepatic Formula
R_x only

DESCRIPTION

Aminosyn-HF 8% (amino acid injection 8%) is a sterile, nonpyrogenic, hypertonic solution for intravenous infusion. The formulation is described below:

Aminosyn-HF 8%
An Amino Acid Injection–Hepatic Formula

Essential Amino Acids (mg/100 mL)	
Isoleucine	900
Leucine	1,100
Lysine (acetate)*	610
Methionine	100
Phenylalanine	100
Threonine	450
Tryptophan	66
Valine	840

*Amount cited is for lysine alone and does not include the acetate salt.

Nonessential Amino Acids (mg/100 mL)	
Alanine	770
Arginine	600
Cysteine HCl • H_2O	<20
Glycine	900
Histidine	240
Proline	800
Serine	500

Electrolytes (mEq/Liter)	
Sodium (Na^+)	11

Phosphate (HPO_4)	20[a]
Acetate ($C_2H_3O_2^-$)[b]	approx. 62[c]
Chloride (Cl^-)	<3

[a] 10 mmoles P/L
[b] Including ions for pH adjustment
[c] From lysine acetate

Product Characteristics per 100 mL

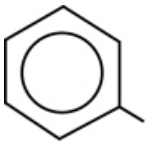
Crystalline Amino Acids	8g
Nitrogen	1.2g[d]
Sodium Hydrosulfite	100mg[e]
Phosphoric Acid	115mg
pH	6.4
pH Range	6.0 to 7.0 [f]
Osmolarity	768 mOsmol/Liter
Specific Gravity	1.02

[d] 7.6g of protein equivalent
[e] Added as the antioxidant
[f] Adjusted with glacial acetic acid

The formulas for the individual amino acids present in Aminosyn–HF 8% are as follows:

Essential Amino Acids

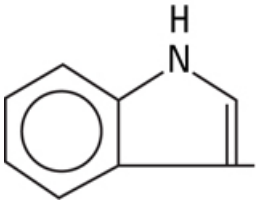
Isoleucine	$CH_3CH_2CH(CH_3)CH(NH_2)COOH$
Leucine	$(CH_3)_2CHCH_2CH(NH_2)COOH$
Lysine (acetate)	$H_2N(CH_2)_4CH(NH_2)COOH \bullet CH_3COOH$
Methionine	$CH_3S(CH_2)_2CH(NH_2)COOH$
Phenylalanine	



$CH_2CH(NH_2)COOH$

Threonine $CH_3CH(OH)CH(NH_2)COOH$

Tryptophan



$CH_2CH(NH_2)COOH$

Valine $(CH_3)_2CHCH(NH_2)COOH$

Nonessential Amino Acids

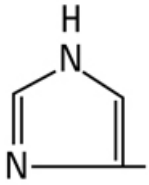
Alanine $CH_3CH(NH_2)COOH$

Arginine $H_2NC(NH)NH(CH_2)_3CH(NH_2)COOH$

Cysteine HCl • H_20 $HSCH_2CH(NH_2)COOH \cdot HCl \cdot H_20$

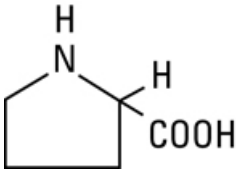
Glycine H_2NCH_2COOH

Histidine



$CH_2CH(NH_2)COOH$

Proline



Serine $HOCH_2CH(NH_2)COOH$

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly.

Solutionsin contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthlate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.
Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period.

CLINICAL PHARMACOLOGY

Aminosyn-HF 8% (amino acid injection 8%) provides a mixture of essential and nonessential amino acids with high concentrations of the branched chain amino acids (isoleucine, leucine, and valine) and low concentrations of methionine and the aromatic amino acids (phenylalanine and tryptophan) relative to general purpose amino acid injections. This amino acid composition has been specifically formulated to provide a well tolerated nitrogen source for nutritional support and therapy of patients with liver disease who have hepatic encephalopathy.
The precise mechanisms which produce the therapeutic effects of Aminosyn-HF 8% are not known. The etiopathology of hepatic encephalopathy is also unknown and is thought to be of multifactorial origin. The rationale for Aminosyn-HF 8% is based on observations of plasma amino acid imbalances in patients with liver disease and on theories which postulate that these abnormal patterns are causally related to the development of hepatic encephalopathy.
Clinical studies in patients with hepatic encephalopathy showed that infusion of a solution identical to Aminosyn-HF 8% reversed the abnormal plasma amino acid pattern characterized by decreased levels of branched chain amino acids and elevated levels of aromatic amino acids and methionine. The trend toward normalization of these amino acids was generally associated with an improvement in mental status and EEG patterns. This clinical response was observed in the majority of patients studied. Nitrogen balance was significantly improved and mortality reduced in these typically protein-intolerant patients who received substantial amounts of protein equivalent from the amino acid solution.
When infused with hypertonic dextrose as a calorie source, supplemented with electrolytes, vitamins, and minerals, Aminosyn-HF 8% provides total parenteral nutrition in patients with liver disease, with the exception of essential fatty acids.
Phosphate is a major intracellular anion which participates in providing energy for metabolism of substrates and contributes to significant metabolic and enzymatic reactions in all organs and tissues. It exerts a modifying influence on calcium levels, a buffering effect on acid-base equilibrium, and has a primary role in the renal excretion of hydrogen ions.
It is thought that the acetate from lysine acetate and acetic acid, under the conditions of parenteral nutrition, does not impact net acid-base balance when renal and respiratory functions are normal. Clinical evidence seems to support this thinking; however, confirmatory experimental evidence is not available.
The amounts of sodium and chloride present are not of clinical significance.

INDICATIONS AND USAGE

Aminosyn-HF 8% (amino acid injection 8%) is indicated for the treatment of hepatic encephalopathy in patients with cirrhosis or hepatitis. Aminosyn-HF 8% provides nutritional support for patients with these diseases of the liver who require parenteral nutrition and are intolerant of general purpose amino acid injections, which are contraindicated in patients with hepatic coma.

CONTRAINDICATIONS

Aminosyn-HF 8% (amino acid injection 8%) is contraindicated in patients with anuria, inborn errors of amino acid metabolism, especially those involving branched chain amino acid metabolism such as Maple Syrup Urine Disease and Isovaleric Acidemia, or hypersensitivity to one or more amino acids present in the solution.

WARNINGS

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.
Because of the potential for life-threatening events, caution should be taken to ensure that precipitates have not formed in any parenteral nutrient admixture.
This product contains sodium hydrosulfite, a form of sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.
Safe, effective use of parenteral nutrition requires a knowledge of nutrition as well as clinical expertise in recognition and treatment of the complications which can occur. FREQUENT EVALUATIONS AND LABORATORY DETERMINATIONS ARE NECESSARY FOR PROPER MONITORING OF PARENTERAL NUTRITION. Studies should include blood sugar, serum proteins, kidney and liver function tests, electrolytes, hemogram, carbon dioxide content, serum osmolarities, blood cultures, and blood ammonia levels.
Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.
Administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, over-hydration, congested states, or pulmonary edema. The risk of dilutional states is inversely proportional to the

electrolyte concentrations of the solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the solutions.
WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.
Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

General
Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.
Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.
Special care must be taken when giving hypertonic dextrose to a diabetic or prediabetic patient. To prevent severe hyperglycemia in such patients, insulin may be required.
Peripheral intravenous administration of Aminosyn-HF 8% (amino acid injection 8%) requires appropriate dilution and provision of adequate calories. Care should be taken to assure proper placement of the needle within the lumen of the vein. The venipuncture site should be inspected frequently for signs of infiltration. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.
Care should be taken to avoid circulatory overload, particularly in patients with cardiac insufficiency.
In patients with myocardial infarct, infusion of amino acids should always be accompanied by dextrose since in anoxia, free fatty acids cannot be utilized by the myocardium, and energy must be produced anaerobically from glycogen or glucose.
Infusion of Aminosyn-HF 8% may not affect the clinical course of patients with fulminant hepatitis who have a poor prognosis and are generally unresponsive to treatment. It has been shown that the abnormal plasma amino acid pattern in fulminant hepatitis differs from that in chronic liver disease.
Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea, or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.
Administration of glucose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma, and death.
Metabolic acidosis can be prevented or readily controlled by adding a portion of the cations in the electrolyte mixture as acetate salts and in the case of hyperchloremic acidosis, by keeping the total chloride content of the infusate to a minimum.
Aminosyn-HF 8% contains no more than 25 mcg/L of aluminum.
Aminosyn-HF 8% contains less than 3 mEq chloride per liter.
Aminosyn-HF 8% contains 10 mMol of phosphate/liter. Some patients, especially those with hypophosphatemia, may require additional phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. To assure adequate intake, serum levels should be monitored frequently.
Aminosyn-HF 8% has not been adequately studied in pregnant women and children; therefore, its safe use in such patients has not been demonstrated.
To minimize the risk of possible incompatibilities arising from mixing this solution with other additives that may be prescribed, the final infusate should be inspected for cloudiness or precipitation immediately after mixing, prior to administration, and periodically during administration.
Use only if solution is clear and container is undamaged. Must not be used in series connections.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Studies with Aminosyn-HF 8% have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy:
Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with Aminosyn–HF 8%. It is also not known whether Aminosyn–HF 8% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Aminosyn–HF 8% should be given to a pregnant woman only if clearly needed.

Nursing Mothers
Caution should be exercised when Aminosyn–HF 8% is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Aminosyn–HF 8% have not been performed to determine whether patients over 65 years respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal functions.

SPECIAL PRECAUTIONS FOR CENTRAL VENOUS NUTRITION
ADMINISTRATION BY CENTRAL VENOUS CATHETER SHOULD BE USED ONLY BY THOSE FAMILIAR WITH THIS TECHNIQUE AND ITS COMPLICATIONS.

Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure, including solution preparation, administration, and patient monitoring. IT IS ESSENTIAL THAT A CAREFULLY PREPARED PROTOCOL, BASED ON CURRENT MEDICAL PRACTICES, BE FOLLOWED, PREFERABLY BY AN EXPERIENCED TEAM.

Although a detailed discussion of the complications is beyond the scope of this insert, the following summary lists those based on current literature.

1. **Technical**

   The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion. For details of technique and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arteriovenous fistula, phlebitis, thrombosis and air and catheter emboli.

2. **Septic**

   The constant risk of sepsis is present during administration of total parenteral nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of the solution and the placement and care of catheters be accomplished under strict aseptic conditions.

   Solutions should ideally be prepared in the hospital pharmacy in a laminar flow hood using careful aseptic technique to avoid inadvertent touch contamination. Solutions should be used promptly after mixing. Storage should be under refrigeration and limited to a brief period of time, preferably less than 24 hours.

   Consult the medical literature for a discussion of the management of sepsis. In brief, typical management includes replacing the solution being administered with a fresh container and set, and culturing the contents for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip is cultured, and a new catheter reinserted when the fever has subsided. Non-specific, prophylactic antibiotic treatment is not recommended.

   Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

   Administration time for a single container and set should never exceed 24 hours.

3. **Metabolic**

   The following metabolic complications have been reported with TPN administration: Metabolic acidosis and alkalosis, hypophosphatemia, hypocalcemia, osteoporosis, glycosuria, hyperglycemia, hyperosmolar nonketotic states and dehydration, rebound hypoglycemia, osmotic diuresis and dehydration, elevated liver enzymes, hypo- and hypervitaminosis, electrolyte imbalances and hyperammonemia in children. Frequent evaluations are necessary especially during the first few days of therapy to prevent or minimize these complications.

   Administration of glucose at a rate exceeding the patient’s utilization rate may lead to hyperglycemia, coma and death.

ADVERSE REACTIONS

See ***WARNINGS*** and **SPECIAL PRECAUTIONS FOR CENTRAL VENOUS NUTRITION.**

Reactions reported in clinical studies as a result of infusion of the parenteral fluid were water weight gain, edema, increase in BUN, and dilutional hyponatremia. Asterixis was reported to have worsened in one patient during infusion of the amino acid solution.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

Symptoms may result from an excess or deficit of one or more of the ions present in the solution; therefore, frequent monitoring of electrolyte levels is essential.

Phosphorus deficiency may lead to impaired tissue oxygenation and acute hemolytic anemia. Relative to calcium, excessive phosphorus intake can precipitate hypocalcemia with cramps, tetany and muscular hyperexcitability.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures, and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE

In the event of a fluid or solute overload during parenteral therapy, re-evaluate the patient's condition and institute appropriate corrective treatment. See ***WARNINGS*** and ***PRECAUTIONS***.

DOSAGE AND ADMINISTRATION

The objective of nutritional management of patients with liver disease is the provision of sufficient amino acid and caloric support for protein synthesis without exacerbating hepatic encephalopathy.

The total daily dose of Aminosyn-HF 8% (amino acid injection 8%) depends on daily protein requirements and on the patient's metabolic and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements. Dosage should also be guided by the patient's fluid intake limits and glucose and nitrogen tolerances, as well as by metabolic and clinical response.

The recommended dosage is 80 to 120 g of amino acids (12 to 18 g of nitrogen) as Aminosyn-HF 8% per day. Typically, 500 mL of Aminosyn-HF 8% appropriately mixed with 500 mL of 50% dextrose supplemented with electrolytes and vitamins is administered over an 8 to 12 hour period. This results in a total daily fluid intake of approximately 2 to 3 liters. Patients with fluid restrictions may only tolerate 1 to 2 liters. Although nitrogen requirements may be higher in severely hypercatabolic or depleted patients, provision of additional nitrogen may not be possible due to fluid intake limits, nitrogen, or glucose intolerance.

In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria. To prevent rebound hypoglycemia, a solution containing 5% dextrose should be administered when hypertonic dextrose solutions are abruptly discontinued.

Fat emulsion co-administration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (EFAD). Serum lipids should be monitored for evidence of EFAD in patients maintained on fat-free TPN. Caution should be exercised in administering fat emulsions to patients with severe liver damage. Fat emulsion may obscure the presence of precipitate formation.

The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is required for optimum utilization of amino acids. Approximately 60 to 180 mEq of potassium, 10 to 30 mEq of magnesium, and 10 to 40 mMol of phosphorus per day appear necessary to achieve optimum metabolic response. In addition, sufficient quantities of the major extracellular electrolytes (sodium, calcium, and chloride) must be given. In patients with hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate salts to provide bicarbonate precursor. The electrolyte content of Aminosyn-HF 8% must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

Hypertonic mixtures of amino acid and dextrose may be safely administered by continuous infusion through a central venous catheter with the tip located in the superior vena cava. Initial infusion rates should be slow, and gradually increased to the recommended 60 to 125 mL/hour. If the administration rate should fall behind schedule, no attempt to "catch up" to planned intake should be made.

In addition to meeting protein needs, the rate of administration, particularly during the first few days of therapy, is governed by the patient's glucose tolerance. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determinations of glucose levels in blood and urine.

For patients in whom the central venous route is not indicated and who can consume adequate calories enterally, Aminosyn-HF 8% may be administered by peripheral vein with or without parenteral carbohydrate calories. Such infusates can be prepared by dilutions of Aminosyn-HF 8% with Sterile Water for Injection, USP or 5% to 10% dextrose to prepare isotonic or slightly hypertonic solutions for peripheral infusion. It is essential that peripheral infusion be accompanied by adequate caloric supplementation.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. COLOR VARIATION FROM PALE YELLOW TO YELLOW IS NORMAL AND DOES NOT ALTER EFFICACY.

Care must be taken to avoid incompatible admixtures. Consult with pharmacist.

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Aminosyn-HF 8% (amino acid injection 8%) is supplied in a 500 mL single-dose flexible plastic container NDC No. 0409-4167-03. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing. However, brief exposure up to 40°C does not adversely affect the product.

Avoid exposure to light.

Revised: June, 2008

Printed in USA EN-1815

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